The Ocular Surface 16 (2018) 198–205

Contents lists available at ScienceDirect

The Ocular Surface

journal homepage: www.theocularsurface.com

Review Article

Effects of environment pollution on the ocular surface

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ARTICLE INFO

Article history:
Received 21 August 2017
Received in revised form
22 January 2018
Accepted 1 March 2018

Keywords:
Human
Review
Ocular disease
Dry eye
Pollution

ABSTRACT

The twenty-first century is fraught with dangers like climate change and pollution, which impacts human health and mortality. As levels of pollution increase, respiratory illnesses and cardiovascular ailments become more prevalent. Less understood are the eye-related complaints, which are commonly associated with increasing pollution. Affected people may complain of irritation, redness, foreign body sensation, tearing, and blurring of vision. Sources of pollution are varied, ranging from gases (such as ozone and NO_2) and particulate matter produced from traffic, to some other hazards associated with indoor environments. Mechanisms causing ocular surface disease involve toxicity, oxidative stress, and inflammation. Homeostatic mechanisms of the ocular surface may adapt to certain chronic changes in the environment, so affected people may not always be symptomatic. However there are many challenges associated with assessing effects of air pollution on eyes, as pollution is large scale and difficult to control. Persons with chronic allergic or atopic tendencies may have a pre-existing state of heightened mucosal immune response, hence they may have less tolerance for further environmental antigenic stimulation. It is beneficial to identify vulnerable people whose quality of life will be significantly impaired by environmental changes and provide counter measures in the form of protection or treatment. Better technologies in monitoring of pollutants and assessment of the eye will facilitate progress in this field.

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1. Introduction

Air pollution is a serious health issue that impacts quality of life, as long term exposure is associated with respiratory and cardiovascular problems [1–3], as well as increased hospital admissions and healthcare spending [4,5]. These phenomena have been observed in the west as well as in Asia [6], and with urbanization, such problems are expected to worsen with time [7]. In severe cases, pollution can even increase mortality [8–10], and adversely affect intrauterine growth [11]. By improving environmental conditions, it has been shown that health indicators can respond favorably [3].

According to the World Health Organization, air pollution consists of different particulate including particulate matter (PM), ozone, carbon monoxide (CO), nitrogen dioxide (NO_2) and sulfur dioxide (SO_2). The number after PM refers to the aerodynamic diameter of the particles; i.e. PM10 refers to particles <10 μm, and PM2.5 refers to particles less than 2.5 μm PM10 is generated from construction and road dust, whilst smaller particles (PM2.5) is derived from combustion sources such as wood and biomass fuels. Regardless of the type of pollutant, pollution is an widespread issue as it can affect *occupations* both outdoors [12] and indoors [13].

Air pollution can affect the eye, causing complaints of eye redness, irritation, watering, foreign body sensation, and blurring of vision; however the link to the environment is sometimes overlooked by eye professionals [14]. Since the ocular surface can be easily examined, it can serve as an indicator of the impact of pollution on health [15,16]. Despite the importance of the effects of pollution on the eye, contemporary research in this area has not been reviewed recently in regards to associations of the types of pollution with clinical signs and symptoms [17,18].

We aim to conduct a literature review of publications in the last 10 years. The search strategy was to retrieve relevant English

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https://doi.org/10.1016/j.jtos.2018.03.001
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articles published in Entrez Pubmed from November 2007 to January 2017, using the keywords “ocular surface”, “pollution”, “dry eye”, “conjunctiva” and “cornea”. Review articles published previous did not have the same scope (individual review described only symptoms or limited to clinical signs) and were not included in this current report [19,20].

2. Environments affecting the eye

Involvement of pollution on the ocular surface has been summarised in 5 population surveys (Table 1). These studies involved whole cities or towns and it is difficult to know which ecosystem within the geographical area is relatively more affected by pollution. These 5 studies were selected as they represent environments where there are chronic exposures to typical pollutants in their respective regions with primary focus on ophthalmic consequences. Therefore, we will next examine studies which specifically address each kind of environment. There can be outdoor pollution from traffic or environmental hazards, and also indoor pollution in the office, or pollution related to occupational activities. It seems that regardless of the type of environment, the reaction of the ocular surface appears quite non-specific in terms of symptoms and signs (described in subsequent sections).

2.1. Outdoors

Traffic-induced pollution is increasingly common in urban populations. Such pollution consists of CO, NO_2 and PM [21]. In Sao Paulo, the major source of air pollution is derived from traffic. *Novaes* et al. [22] studied 55 healthy volunteers who have been living in the study area for at least 5 years. The participants were each given a passive NO_2 monitoring apparatus to be carried by participants for a period of time while doing their daily activities [22]. In this study, it was noted that an increase in exposure to NO_2 was correlated to rise in frequency of irritative dry eye symptoms. This corresponded to decreased tear break up times (TBUT), a measure of tear stability, and increased frequency of meibomitis, which is a condition characterized by occlusion of the oil-producing meibomian glands. Unfortunately, the authors did not describe the system of grading for the meibomitis, except that it was a finding on slit-lamp biomicroscopic examination. Their finding is also supported by another team studied in Sao Paulo [23] that combustion-derived pollutants are associated with increased meibomian gland secretion and eyelid debris, causing blepharitis. The driving force is thought to be due to overloading of antioxidative defense system on the eyelid margin causing changes in the structure of essential fatty acids and chronic inflammation [17,23].

Furthermore in the study, *Novaes* et al. did not determine the mechanism for traffic-related air pollution on tear stability, however a strength of the study is that the level of NO_2 in the air was objectively measured individually. Despite these shortcomings, the authors concluded that the conjunctival mucosa may be a bio-indicator of environmental pollution.

A much larger study ($n = 16824$) conducted in Korea also reported the effect of outdoor pollution on the ocular surface [24]. This study was performed over 3 years (2010–2012), using a stratified multi-stage clustered sampling method based on national resident demographics, achieving a participation rate of 80.8%. 6263 participants lived in an urban environment, whereas 7560 lived in a rural environment, and environmental data were gathered at 283 atmospheric monitoring stations. As this was a population-based study unlike the study in Brazil, no personal monitoring device was used for measuring pollutant level. All participants were asked if they either had symptoms of dry eyes (e.g. eyes feel dry or irritated), or if they have been diagnosed with dry eyes. The advantages of using a large sample size included the possibility of logistic regression which adjusted for many confounding variables, including the effect of multicollinearity between variables. This study found that increased ozone levels and reduced humidity were associated with dry eye, after controlling for sex, dyslipidemia, thyroid disease, subjective health awareness and previous ocular surgery. NO_2 but not PM10, was associated with dry eye. Although the PM10 levels in this study were higher than the levels recommended by the World Health Organization ($20\ \mu g/m^3$), the authors speculated that reflex tearing may have protected participants from the adverse ocular surface effects. The major limitations of the study were that ocular surface examination was not performed, specific symptoms of dry eyes, such as blurring of vision, pain, redness, irritation were not explored, PM2.5 data were not available, and seasonal variation of air pollutants was not analysed.

Similarly, when an environmental hazard occurs such as a *trans*-boundary haze (defined as haze arising from a source across national borders), health in populations is affected. This may occur when there is a tremendous increase in burning of forested lands for the purpose of agriculture or other developments, like in Sumatra, Indonesia. Such haze often extends to neighboring and sometimes faraway countries. In affected countries, this haze has been shown to cause irritative symptoms affecting the eyes, mouth, throat, nose, as well as induce headaches, breathing problems, and psychological stress [25].

2.2. Indoors

Office eye syndrome was first introduced in 1986, and described as eye irritation associated with indoor climate problems [26]. Dry eye complaints in office workers is chronic but without seasonal variations. Factors that affect the pre-corneal tearfilm may be humidity, temperature, individual risk factors and certain occupational tasks such as computer use. The low relative humidity in offices, if sustained, increases evaporative rates of aqueous tear. Visual display units can also destabilize the tearfilm because of reduction of blink frequency and increase in the palpebral aperture, which results in a larger area of ocular exposure to the environment. It was reported that 25% of 169 office workers in Copenhagen had eye irritation and unstable pre-corneal tearfilm, but this has not been compared to another reference group [21,27].

There was a study that reported alteration in tear function of hospital workers in air-conditioned environment for up to 4 years, with un-exposed people as controls. The authors reported that symptoms and signs might have plateaued at 2–4 years of exposure. However, this is not a longitudinal study and there may be other confounding factors such as differential use of relieving eyedrops [28]. Cleanliness of the office also affects tearfilm via accumulation of dust on the floor [29,30], and can result in allergic reactions against house dust mites and their excreta [31]. Using a questionnaire, the perceptions of coldness and air dryness have also been found to be significantly associated with eye irritation [30].

Another work-related activity that can induce ocular symptoms is chimney sweeping. Recently, the black-soot sweeping industry has been linked to occurrence of eye and nasal symptoms and coughing. Such workers had an increased risk of eye symptoms (running, itching, stinging, burning) with an odds ratio of 3.76 (95% Confidence interval: 1.72–8.24) with every 10% increment of exposure to soot. Fortunately, the number of chimney sweepers exposed to black soot over the last few years has decreased, due to a change in the type of fuel for heating buildings and not using actual fires [32]. There have been reports of eye symptoms linked to increased years of welding. A study conducted in Sweden shows that symptoms increase during working days. The irritants in the

Table 1
Summary of clinical studies.

Study	Setting, Country	Study design	Participant type	Sample size	Dry eye parameters	Environmental monitoring	Findings	Bias and Possible confounding
Longo BM. 2009	Hawaii, United states	A cross- sectional, environmental epidemiological, and qualitative design	Health data were collected in participants' homes using an interview and assessment conducted in English or Tagalog by the nurse investigator	335 participants	Reporting complaints of eye irritation	SO2 using a regional network of 70 SO2-specific passive diffusion tubes - Outdoor tubes sampling cross sectional pattern to volcanic plume - Indoor tubes in homes and facilities	Eye irritation: Adjusted odds ratio 95% CI 6.89 (3.27−14.52)	No reference group
Gupta et al., 2007 [35]	New Delhi, India	Cross sectional study with ad-hoc comparison group	Volunteers (>18 years age) who commuted daily through highly polluted areas at least 2 years, Controls: housewives and people residing on campus of 3 research centers.	441(study group); 79 (control group)	Symptoms of dry eye (redness, watering, irritation, strain, blurring, photophobia) Schirmer test (5min, >10 mm is normal) TBUT[a] (mean of 3 blinks, >15 s normal); Presence of particulate matter.	Not performed in same study Parameters measured: Age, sex, profession, distance travelled, commuting time, mode of transport, period of daily travel, route.	*Symptoms:* 78% (study group) 45% (control group). ($p < 0.001$) *Schirmer's test:* 22.75 ± 8.91 mm (study group), 30.30 ± 7.92 mm (control) ($p < 0.001$). TBUT: 11.17 ± 2.92 (study group) 12.13 ± 2.92 (control group) ($p < 0.05$)	Comparison groups not gender matched. History of pre-existing allergies (atopy, asthma, sinusitis) not evaluated. Potential dietary factors (eg., omega-3 fatty acids) and other factors (sleep) not evaluated.
Novaes 2010 [22]	Sao Paulo, Brazil	Cross sectional study	Healthy volunteers (staff of general clinic hospital) in study area for at least 5 years.	55	OSDI, symptoms (ocular dryness, irritation, heaviness/ fatigue and itching) TBUT; Schirmer I test; Staining (fluorescein, rose bengal).	Mean daily exposure to NO_2[b] (1 week of NO_2 exposure divided by 7). PM10 concentration (Beta monitor, NO_2 levels- passive tube system) for 3 weeks. Correlation between PM[e]10 and NO_2 levels: $R = 0.95$.	TBUT 6.8 ± 4.6 s. Dose−response between OSDI and NO2 ($p < 0.05$). Association between NO_2 and ocular irritation ($X^2 = 9.2$, $p < 0.05$). Inverse association NO_2 and TBUT ($p < 0.05$, $R = -0.31$). Association of increased meibomitis with higher NO_2 ($p < 0.05$) No correlations between NO_2 and Schirmer I or Staining.	No reference group
Torricelli 2013 [37]	Sao Paulo, Brazil	Cross-sectional study	71 (taxi drivers and traffic controllers) in study area for at least 5 years.	71	OSDI, TBUT, Schirmer test, staining (cornea, conjunctiva), tear osmolarity	24-h exposure of NO_2 and PM2.5	TBUT reduced, staining and Schirmer within normal	No reference group; short study
Torricelli 2014 [47]	Sao Paulo, Brazil	Cross sectional study	Healthy male volunteers (taxi drivers or traffic controllers) in study area ≥ 5 years.	21 male subjects, 31 −57 years	OSDI[c] Symptoms of ocular dryness, irritation, heaviness, fatigue, itching over preceding 7 days. Impression cytology for: Conjunctival goblet cell assays MUC5AC[d] assays	NO_2 and PM2.5- NO_2 passive tubes. Accuracy of 98.6% precision of 80% [4] Particulate matter sampled with a personal gravimetric particulate impactor [56] Subjects carried sampler for 24 h	Positive association between a. MUC5AC mRNA levels and tarsal GC density ($R = 0.56$, $p = 0.023$) b. PM 2.5 levels and tarsal GC density ($R = 0.49$, $p = 0.052$) After excluding 1 patient with tarsal GC density of 1208 cell/ mm^2 and PM2.5 of 22 $\mu g/m^3$ ($R = 0.67$, $p = 0.005$). OSDI/MUC5AC mRNA levels not correlated with PM2.5 and NO_2 levels	Can generalize to other settings? Gender bias- only male Study conditions: Ambient temperature (18.2 −23.1 °C) Air humidity (55%-76% mean $64 \pm 6\%$) PM2.5 (35 ± 12 $\mu g/m^3$) NO_2 (189 ± 47 $\mu g/m^3$) Compliance of carrying sampler monitored?
Wiwatanadate P 2014 [43]	Chiang Mai, Thailand	Cross sectional study	Population based survey Eligibility criteria 1. Age greater than 14 year old 2. Non smoker 3. Lived in Mae Rim for more than 1 year	3025 total (1001 male, 2024 female)	Symptoms: • Burning or itching eyes • Red eyes • Watery eyes • Blurred vision	Measured by Pollution Control Department, Ministry of National Resources and Environment with continuous automated air sampling monitoring station at centre of city. CO: Nondispersive infrared detection SO_2: Pararosaniline technique NO_2: Chemiluminescence technique	PM_{10} was significantly positively associated with blurred vision with adjusted OR of 1.009 (95% CI = 1.004 to 1.014) per 1 $\mu g/m^3$ NO2 significantly positively associated with eye irritation with adjusted ORs of 1.051 (95% CI = 1.032 to 1.070) per 1 part	Inclusion criteria- does not specify those who may commute out of the region

						O_3: Chemiluminescence technique PM_{10}: Gravimetric technique All techniques certified by U.S. Environmental Protection Agency	per billion (ppb). SO2 concentrations were significantly positively associated with • eye irritation 1.264 (95% CI = 1.085 to 1.471) • Red eyes 2.948 (95%CI = 1.463 to 5.940) • Blurred vision 1.210 (95% CI = 1.004 to 1.459) per 1 ppb O3 concentrations were negatively associated with • red eyes adjusted ORs of 0.891 (95%CI = 0.847 to 0.938), • blurred vision adjusted ORs of 0.962 (95% CI = 0.947 to 0.977) per 1 ppb	
Hwang et al., 2016 [24]	South Korea	Cross sectional study	Population-based survey held from 2010 to 2012. Only adults included?	16824 (total): 7104 (men), 9720 (women).	Epidemiologic survey (dryness, irritation, or existing diagnosis of dry eye syndrome)	PM10, ozone, NO_2, SO_2,[g] relative humidity.	*Increased ozone* 0.003 ppm associated with DED[f] - Symptoms: OR[h] 1.16 (95%CI[i] 1.02−1.30); - Diagnosis: OR 1.21 (1.05 −1.40). *Increased humidity (by 5%)* associated with decreased DED - Symptoms: OR 0.87 (0.77 −0.98); - Diagnosis: OR 0.86 (0.76 −0.97). *Increased NO_2* 0.003 ppm associated with DED - Diagnosis: OR 1.12 (1.02 −1.23). *SO_2 and PM10* levels not associated with DED symptoms or diagnosis.	Inclusion of people with known causes of dry eye (e.g. Sjogren's syndrome) may complicate interpretation, although adjusted for.

1. Longo BM. The Kilauea Volcano adult health study. Nurs Res 2009; 58:23−31.
2. Torricelli AA, Novaes P, Matsuda M et al. Correlation between signs and symptoms of ocular surface dysfunction and tear osmolarity with ambient levels of air pollution in a large metropolitan area. Cornea 2013; 32:e11−e15.
3. Torricelli AA, Matsuda M, Novaes P et al. Effects of ambient levels of traffic-derived air pollution on the ocular surface: analysis of symptoms, conjunctival goblet cell count and mucin 5 A C gene expression. Environ Res 2014; 131:59−63.
4. Novaes P, do Nascimento Saldiva PH, Kara-Jose N et al. Ambient levels of air pollution induce goblet-cell hyperplasia in human conjunctival epithelium. Environ Health Perspect 2007; 115:1753−1756.
5. Hwang SH, Choi YH, Paik HJ et al. Potential Importance of Ozone in the Association Between Outdoor Air Pollution and Dry Eye Disease in South Korea. JAMA Ophthalmol 2016.

[a] TBUT: tear break up times.
[b] NO: nitrogen oxide.
[c] OSDI: ocular surface disease index.
[d] MUC: mucin.
[e] PM: particulate matter.
[f] DED: dry eye disease.
[g] SO: sulfur oxide.
[h] OR: odds ratio.
[i] Confidence interval.

air are produced from welding and grinding. Therefore, it is necessary to offer regular medical surveillance and provide protective equipment to welders [33].

3. Methodologies of research and advances

3.1. Methods of assessing ocular surface

There are a variety of methods for assessing effects of environment on the ocular surface. The biggest complaint is dry eyes are the symptoms are measured with different scoring questionnaires available, such as the Ocular Surface Disease Index (OSDI), Standard Patient Evaluation of Eye Dryness (SPEED) and Symptom Assessment iN Dry Eye (SANDE). These questionnaires assess the reported frequency of eye irritation, dryness, tearing or blurring of vision. These standardized questionnaires make it fair for comparison of effects from different environments triggers [34]. In addition to subjective symptom assessment, clinical examination and various diagnostic tests are conducted to quantify tear and ocular surface function. To assess ocular surface disease, slit-lamp biomicroscopic examination of ocular adnexa, conjunctiva and cornea is used. Tear film stability (e.g., TBUT) and corneal staining with either fluorescein, Rose Bengal or lissamine green dyes can be done. Diagnostic tests include schirmers test, lysozyme activity [35,36], osmolarity assay [37], and impression cytology [38]. Impression cytology performed on people exposed to pollution can show goblet cell hyperplasia [15], as well as inflammatory cells [39] in the conjunctiva. Messenger RNA can be extracted from such goblet cells to assess the expression of mucins, including the gel-forming mucin MUC5AC [40–42]. The latest article from TFOS DEWSII report summarizes all the common methods of assessing dry eyes [34].

3.2. Methods of assessing pollution

In certain countries, large databases allow the monitoring of pollution data which maybe useful for correlation to ocular features. For example in Thailand, in areas where they are annually affected by the smog crisis such as in Mae Rim, the Pollution Control department by Ministry of National Resources and Environment has continuous automated air quality monitoring station in the centre of the district. They monitor CO concentrations using nondispersive infrared detection, SO_2 concentrations by pararosaniline technique, NO_2 and O_3 concentrations from chemiluminescence technique and PM_{10} with gravimetric technique. These monitoring techniques are certified by the U.S Environmental Protection Agency [43].

Whereas in Korea, there were several hundred atmospheric monitoring station controlled by Korea Ministry of Environment has air pollutants and meteorologic data base including PM10, O3, NO2, SO2, and relative humidity. Some of the pollutants are measured similarly where PM10 is measured with a β-ray absorption technique, O3 using a UV photometry, NO2 with chemiluminesce and SO2 with pulse UV fluorescene technique [24].

In cases where pollutants are monitored individually, PMs may be measured by membranes or light scattering methods for individuals. In contrast, gases such as NO_2 can be measured by a passive sampler made of a cellulose filter impregnated with an absorbant solution—trietanolamine 2%, 0.05% o-methoxyphenol, and 0.025% sodium metabisulfite in a small plastic tube with one of end open to the environment. The nitrite produced during sampling of air can be determined colorimetrically by mixing the exposed absorbing reagent with sulfanilamide and 8-anilino-1-naphthalenesulfonic acid (ANSA) at a wavelength of 550 nm [15].

4. Mechanisms

Some mechanisms causing ocular surface problems are toxicity, oxidative stress, and inflammation from gases and traces of particles in the atmosphere (Fig. 1).

4.1. Gases

The gaseous pollutant SO_2 is derived from fossil fuel and biomass combustion. When sulfur-containing gases are solubilized, they could result in formation of sulfurous or sulfuric acids, which can subsequently react with bases forming sulfates. Per-sulfate can be an *irritant or sensitizer* and this is associated with occupational asthma [44]. It can also behave like a *hapten*, which sensitizes the skin of some people such as hairdressers, resulting in contact dermatitis [45]. The conjunctiva of the eye contains various antigen presenting cells (Langerhans cells and dendritic cells), which may present antigens and haptens to naïve T lymphocytes in the ocular surface or regional lymph nodes to mount an immune response. Subsequently, activated T cells would specifically target the ocular surface tissues which have been sensitized. Immune-mediated destruction of the conjunctiva epithelium will reduce tear and mucin production, which clinically impair tear stability and cause dry eye. Some of the T cells would remain chronically as memory cells, on the ocular surface and in blood circulation, after the initial activation. These retain specificity to the original antigens and would make subsequent exposures more likely to trigger severe allergic disease.

When atmospheric SO_2 is increased, there is a drop in tear pH [46]. This may irritate the eyes as there are many afferent corneal nociceptors that are sensitive to acidification of tears, and the impulses from these neurons will be perceived as pain. However over the years, the sulfur content in biofuels are decreasing, so the overall impact of SO_2 on general health may not be as severe as initially expected [13].

Exposure to high levels of another gas, NO_2, induces goblet cell hyperplasia in the tarsal conjunctiva [15]. The molecular mechanism is not well-known. Importantly, people exposed to NO_2 are also exposed to small particles (PM2.5) so it is not easy to determine which of these are responsible for the observed changes in the tarsal goblet cell density. Whatever the initial cause, MUC5AC mRNA levels were also positively correlated to the increased goblet cell density [47]. The increase in MUC5AC may be an adaptive response to chronic exposure, helping with ocular surface homeostasis, and may actually alleviate symptoms after exposure to pollution for some time.

An important class of pollutant from vehicle exhaust gases and second hand cigarette smoke includes the volatile aromatic organic compounds (VOC) and ammonia. Examples of VOC include methane, benzene, and chloroflurohydrocarbons. Some polycyclic aromatic hydrocarbon gases have been known to be teratogenic in living cells. Within organic compounds, the most toxic would be dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin), which would induce cytotoxicity. However this could bind to Aryl Hydrocarbon Receptor (AhR) in human cells, and initiate down-stream signaling to dioxin response elements that would increase certain cellular defenses to oxidation, inflammation and apoptosis [48].

The action of sunlight on VOCs and nitrogen oxides can form peroxyacetyl nitrate (PXN) or ozone, other common air pollutants. PXN has also been shown to have similar effects as VOCs [49]. Long-term contact with ozone, on the other hand, can result in *oxidative damage* or *peroxidation* of biomolecules [49]. Oxidative damage and activation of stress pathways such as NF-κB can increase production of inflammatory cytokines. These processes can break down corneal epithelial integrity and reduce mucin-secreting cells [50].

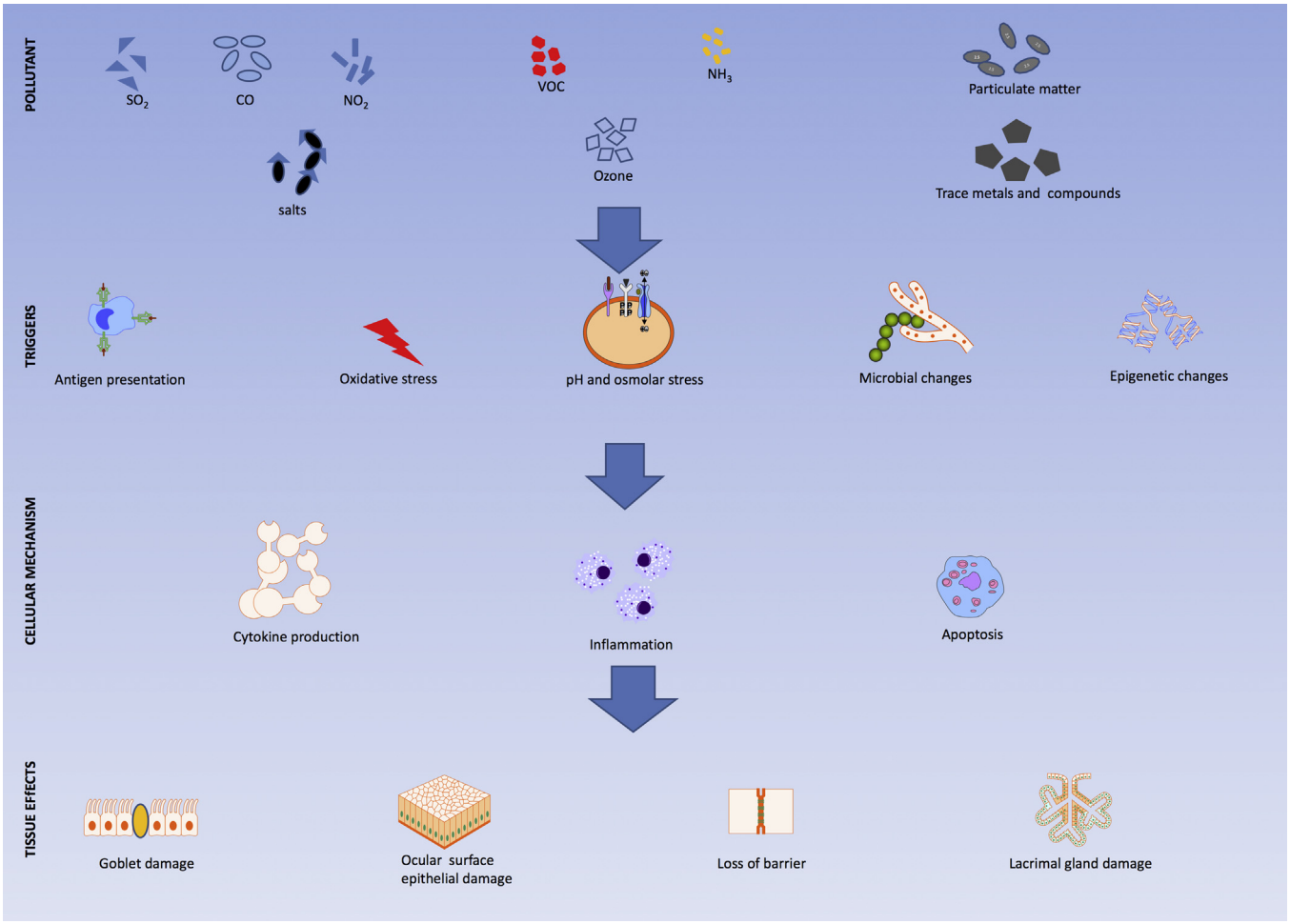

Fig. 1. Schematic showing the mechanism of pollutants (gases and particulate matter) inducing pathology in the ocular surface. Any one stimulant upstream can be combined with another trigger to lead to the downstream processes (for simplicity, cross-crossing arrows are not shown). SO_2: Sulfur dioxide, CO: carbon monoxide, NO_2: nitrogen dioxide, VOC: aromatic volatile organic compounds and NH_3: ammonia.

Ozone has been especially linked to an over-expression of conjunctival IL-6 and tumour necrosis factor-α, which results in allergic ocular signs such as chemosis, conjunctival injection, ocular surface dye staining, and reduced tear volume [51].

4.2. Metals and particulate matter

Metals (such as iron and nickel), biological agents (plant pollen, endotoxins, bacteria) and minerals (quartz, asbestos) form PMs. Trace metal compounds such as aluminium tetrafluoride and manganese compounds are correlated with ocular symptoms, but the molecular mechanisms for such correlations are not understood [52]. In a study, 28% of welders have complained of ocular symptoms due to high exposure to manganese and gases [53]. Exposure to welding fumes does not only irritate the lungs, but the irritation of the respiratory and nasal mucosa spreads secondarily to the ocular surface.

A possible mechanism of titanium oxide (TiO_2) in pollution is induction of epigenetic changes such as expression of pathological microRNAs and methylation of DNA [54,55], but this phenomenon has not been evaluated in the context of the ocular surface. Aerosols and soil bacteria could have metabolites that influenced the microbiome colonies on the surface of eye [56]. Since it has been reported that exogenous bacteria administration influenced the severity of allergic conjunctivitis [51], changes in ocular microbiome may have secondary immune-regulatory effects, which are currently poorly studied. The secondary changes of the immune response may be originating from oxidative stress, pro-inflammation, changes in the intracellular proteins, stimulation of the autonomic nervous system receptors, and suppression of the normal defense mechanisms [17].

Individuals initially exposed to high levels of PM2.5 have increased tear osmolarity. This increased osmolarity triggers many pathways in the corneal epithelial cells, including the mitogen-activated protein kinases and expression of many cytokines [57–59]. These changes would increase ocular surface inflammation and predispose to dry eye. Chronic exposure to suspected PM can induce changes in the ocular surface as some may remain as suspended particles [37]. The pollutant can be thought to have an incubation from their lagged effects [43]. After chronic exposure, the tearfilm osmolarity may normalize to some extent, which can produce paradoxical results, making it difficult to determine the relationship between exposure dose and the effect on tear osmolarity. Small PMs, compared to larger-sized PM, are less likely to directly impact on tear secretion and epithelial barrier function [37].

An animal experiment done on rats shows titanium dioxide nanoparticles as a particulate matter damages the ocular surface secondary to increased tear lactate dehydrogenase level and inflammatory cell infiltration [60]. Likewise, in another animal

experiment on mice with Sjoren's syndrome, residual oil fly ash was used as a particulate matter. In the lung histology of mice which were exposed to particulate matter, there were lymphocytic peribronchial infiltrates exacerbating pre-existing pulmonary lesions [61].

5. Challenges

5.1. Human studies

Limitations exist in human studies, as air pollution is very difficult to control and standardize. Many different living and environmental factors exist in a polluted city, and some may be unrelated to the pollution. For example, people may be living in a more stressful environment or have less time for physical exercise and proper diet. Potential confounding factors also include seasonal effects like atmospheric pollen exposure and genetic differences. In addition, large population studies involve a higher number of participants and time may be limiting so it is more challenging to conduct detailed examinations. In a questionnaire-based study, there could be under or over-reporting of symptoms [24]. As these studies are cross-sectional in nature, they cannot establish a cause and effect relationship but only an association between pollution and dry eye symptoms.

Objective measurements of pollutant levels in the environment are a necessary adjunct to participant's recalling period of exposure to at-risk environments/activities. However, resources may allow measurement of only one particular type of pollutant which may not be representative of the total amount of pollution participants are exposed to. In addition, there is no standardized methodology for evaluating *ocular response* to environmental hazards thus it is difficult to compare between studies.

5.2. Obstacles in animal studies

Animal studies can create a more controlled environment. However one of the limitations of animal studies is that often the exposure levels are very high and these are not expected in actual human scenarios. A study done by *Anderson* et al. [62] showed that air-borne emissions from commercial products (fabric softeners, disposable diapers, and vinyl mattress covers) for 2–3 h can result in sensitivity reactions in mice. However, the response is measured as pneumo-tachographic changes, *i.e.,* respiratory rather than ocular changes, though the two are often associated. It is also difficult to assess long-term changes, including adaptive changes in animal studies, due to relative short time frame of experiments. Animal experiment results may not be extrapolated to humans because chronic sensitization and mucosal immune responses in human take some time. In addition, there are differences in the immune response between human and mice. In mice, the eyes are smaller so it is more difficult to phenotype morphological changes or functional changes, and the minute amount of tear is challenging to analyse. In terms of methodology, PM suspensions in general, may be a challenge to standardize in a laboratory condition for repeated testing. All these factors should be considered when interpreting results.

Even if the biomedical impact of pollution is supported by strong experimental evidence, challenges to managing air pollution still exist due to sociopolitical concerns. The government and individuals have to set priorities and goals to maximize net benefits to society, as certain parties will perceive these efforts to be conflicting with industry, agriculture and other commercial interests [63]. Future studies should focus on the total contribution of ocular disease to overall cost of pollution. This includes not just morbidity of ocular disease but also the detrimental economic effect of loss of productivity and time off-work.

6. Conclusion

Air pollution has a significant impact on ocular surface, and in people predisposed to immune triggers, it is likely to incur marked morbidity and reduce quality-of-life. Although the loss of immune tolerance and involvement of pro-inflammatory cytokines are suspected to play a role, the *detailed* mechanisms through which air pollutants interfere with tear film, cornea and conjunctiva still remain unclear. At the present moment, it is unclear if the composition or the immunological regulatory behavior of the microbiota residing on the ocular surface is affected by pollution. There needs to be more studies that comprise larger groups of participants exposed to different levels of pollution, which can document acute effects as well as potential compensatory responses. There should be standardized methods to assess pollution in different areas around the world. Better technologies in the future, such as analytical platforms and biophysical tools will help to address some of these questions. For example, ionic liquid technology can be used to recover VOCs [64].

For certain occupations that necessitate higher exposure to irritants, ocular effects of pollution should be screened for regularly, and during pre-employment checks. In cases where exposure is unavoidable, protective measures should be used and provided by the employers, government or other relevant bodies. Screening should also be performed for the risk factors that may aggravate the effects of pollution, these include, for example, underlying atopy, sinusitis or allergic tendencies. Identification of susceptible individuals requiring early treatment is likely cost-effective and beneficial to prevent chronic ocular disorders characterized by more established immune responses.

7. Conflicts of interest

Nil.

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